

Appln No.: 09/689,992

Applicate Craig C. Mello et al.

RNA IN FERENCE PATHWAY GENES AS TOOLS FOR TARGETED GENETIC INTERFERENCE

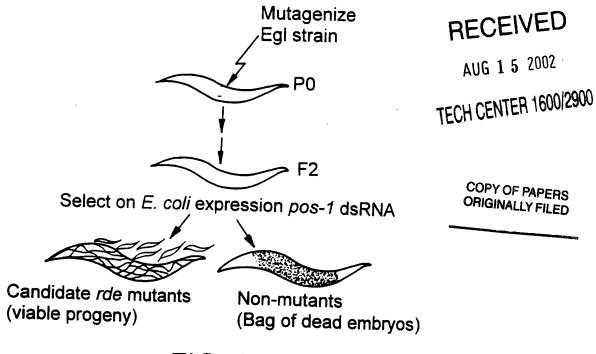


FIG. 1A

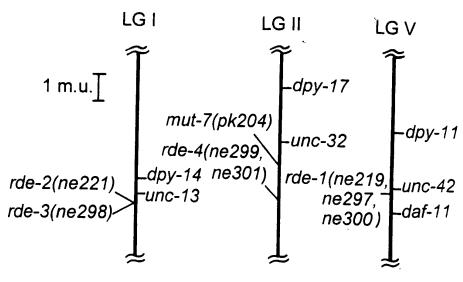


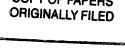
FIG. 1B

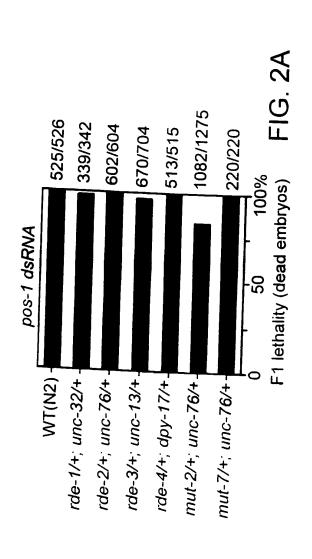


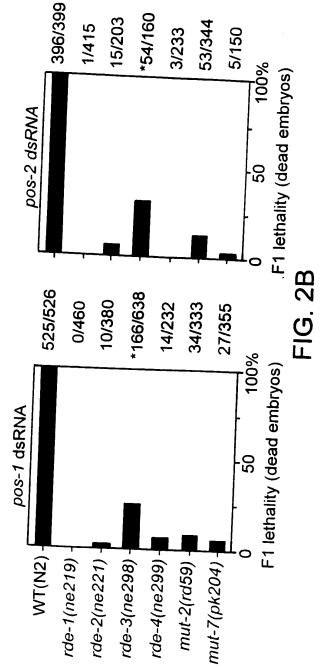
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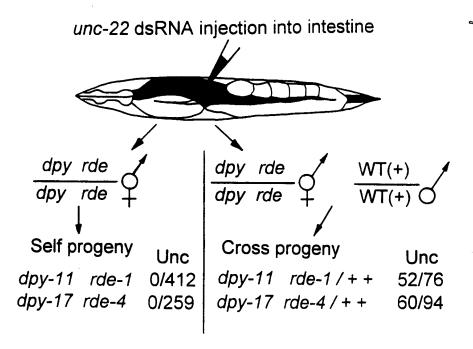


FIG. 3



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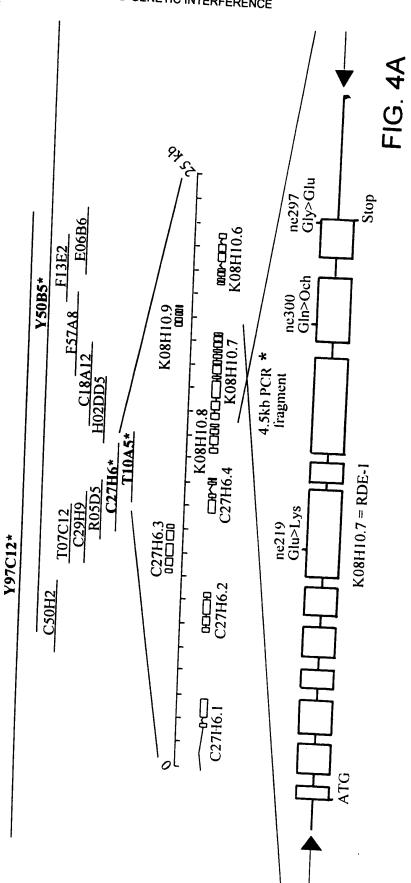
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QLNVVPEKELCCAVE <u>VVN</u> ETAGNPCLEBNBVVKFYTBIIGGGKFREIRIGANENRGAOSIMYBATKNEMAFYKNCTLNTGIGRFEIAATE RGKOFHTGIDVRYWAIAGFAO-DOHYKBNDLRMFTNOLORISNBAGAPIVGNPGRCKYAVGVEOVEPMFYYKONYSG	AKNMFERLPDKEQKVEMFIFISKRQINAFGEVKHYCDHTIGVANOHIFISETVTKALASLRHEKGSKRIFYQIAKINAKIGGINDELDWS - IQLVVVVTBG-KTEVYAEVKRYGDTT GVANOCYGAKNAIRTRP - GYLBNIC HYNNKIGGINSILLEN - GYLBNIC HYNNKIGGINNITILEN - DPQIVMYVRSPNEEKYSCI KRTCVDRPVPSOCYCHTHVITEN - DPQIVMYVRSPNEEKYSCI KRTCVDRPVPSOCYCHTHVITEN - TRIBLE SPEEKERRTMPLTZYWGIDVTHPTSYSGIDYSTAAVVASINPGGT-INRNMIVTOEECRPGERAVEHGRE-RTDILEAKFVK - RPPIFOOPYTETGADVTHPRAGDSKRPSTAAVVSSADAHPR-RYKVOOHROEITSDLTY
514 581 392 542 482	604 658 469 620 552 694 725 536 691 621
RDE-1 F48F7.1 eIF2C ZWILLE Sting	RDE-1 F48F7.1 eIF2C ZWILLE Sting RDE-1 F48F7.1 eIF2C ZWILLE Sting



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SKICHTHMYYN OKLDEIYKSAGKQEGC-RMTETIVSKRINSRYFTGHRUPV---(SEQUID NO: SEQUID NO: E ne297 SINSEVKOFMSERDGEDPEPKY RP CAL REDYOPG ----T REACMALERGYOPG----DKLIVSKYKEDFFL DVGITHPTEFDFYL DYKITHFTEFDFYL DYKICHPTEFFFL YAHKLAFLVABSINRAPSAGLONOLYFL-----AETDVAVAAVKQWEEDMKESKETGIV<mark>N</mark>PSS<mark>GVYVD</mark>I SGTURVE GTRSVS. CTRSVS1 603 775 687 868 619 853 766 936 747 827 921 F48F7.1 F48F7.1 F48F7.1 ZWILLE ZWILLE Sting ZWILLE eIF2C Sting eIF2C Sting eIF2C

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cage cacaaagtgatgaaacatgteetegaatttteeegaattggaaaaggattttategteattetetegateeggta

FIG. 5A

ataataataateaeeteaaeteatttatatattttaagaeaattegegaaaaattttgtgtaegataataatteaat



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tanactttengaacaacgacaategageaceagegeatattgtagtetategagaeggagttagegatteggagatgeta

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cgtgttagtcatgatgagcttcgatctttaaaaagcgaagtaaaacaattcatgtcggaacggatggagaagatccaga geegaagtaeaegtteattgtgatteagaaaagaeaeaaataeaegattgettegaagaatggaaaagataageeagtg lenntanagatettaeteetgetgannengutgtegetgttgetgetgttanaenatgggaggaggatatgaaagaaage attaigeteatttateatgigaaaaagegaaagagetttategaaettaeaaggaaeattaeateggigaetatgeaeag naagaaactggaattgtgaacccatcatccggaacaactgtggataaacttatcgtttcgaaatacaaattcgatttttt ccacggactcgacacgaaatggaacattttctccaaactaacgtgaagtaccctggaatgtcgttcgcataacattttgc uugatgaagtetatgtaagegttttgaatageagttagegattttaggattttgtaateegeatutagttattataaaa ualgitticagaaaatgacciacggactigctittetetetgetagatgtegaaaaeeeatetegtigeetgtteeggtte FIG. 5C cattecatgaetaaegtttteataaattaettgaaattt (SEQ ID NO:1)

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CAGCCACAAAGTGATGAAAC- 5/UTR

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1/1 31/11 ATG TOO TOG AAT TIT COO GAA TITG GAA AAA GGA TIT TAT CGT CAT TOT CTC GAT COG GAG Met ser ser asm pne pro glu leu glu lys gly pne tyr arg his ser leu asp pro glu 61/21 91/31 ATG AAA TGG CTT GCG AGG CCC ACT GGT AAA TGC GAC GGC AAA TTC TAT GAG AAG AAA GTA met lys trp leu ala arg pro thr gly lys cys asp gly lys phe tyr glu lys lys val 121/41 STT STT TTG GTA AAT TGG TTS AAG TTS TSS AGS AAA ATT TAS GAT SGG GAA TAS TAS GAG 151/51 leu leu leu val asn tro phe lys phe ser ser lys ile tyr asp arg glu tyr tyr glu TAT GAA GTG AAA ATG ACA AAG GAA GTA TTG AAT AGA AAA CCA GGA AAA CCT TTC CCA AAA 211/71 tyr glu val lys met thr lys glu val leu asn arg lys pro gly lys pro phe pro lys 271/91 AAG ACA GAA ATT CCA ATT CCC GAT CGT GCA AAA CTC TTC TGG CAA CAT CTT CGG CAT GAG lys thr glu ile pro ile pro asp arg ala lys leu phe trp gln his leu arg his glu 301/101 331/111 AAG AAG CAG ACA GAT TIT ATT STS GAA GAC TAT STT TIT GAT GAA AAG GAC ACT GTT TAT lys lys gin thr asp phe ile leu glu asp tyr val phe asp glu lys asp thr val tyr 361/121 391/131 AGT GTT TGT CGA CTG AAC ACT GTC ACA TCA AAA ATG CTG GTT TCG GAG AAA GTA GTA AAA ser val dys and leu asn thr val thr ser lys met leu val ser glu lys val val lys 421/141 451/151 lys asp ser glu lys lys asp glu lys asp leu glu lys lys ile leu tyr thr met ile 481/161 STT ACC TAT CGT AAA AAA TTT CAC CTG AAC TTT AGT CGA GAA AAT CCG GAA AAA GAC GAA leu thr tyr arg lys lys phe his leu asm phe ser arg glu asm pro glu lys asp glu 541/181 571/191 GAA GCG AAT CGG AGT TAC AAA TTC CTG AAG AAT GTT ATG ACC CAG AAA GTT CGC TAC GCG glu ala asn arg ser tyr lys one leu lys asn val met thr gln lys val arg tyr ala 631/211 COT TIT GIG AAC GAG GAG ATT AAA GIA CAA TIC GCG AAA AAT TIT GIG TAC GAT AAT AAT pro phe val ash glu glu ile lys val gin phe ala lys ash phe val tyr asp ash ash 661/221 691/331 TOA ATT OTG OGA GTT OOT GAA TOG TIT DAG GAT OOA AAC AGA TIG GAA DAA TOA TIA GAA ser ile leu arg wal pro giu ser phe his asp pro asn arg phe giu gin ser leu giu 721/241 751/251

FIG. 6A

3 3 TARGETED GENETIC INTERFERENCE

GTA GOA COA AGA ATO GAA GOA TGG TTT GGA ATT TAC ATT GGA ATO AAA GAA TTG TTC GAT wal ala pro arg lie glu ala trp phe gly lie tyr lie gly lie lys glu leu phe asp

GGT GAA COT GTG CTC AAT TIT GCA ATT GTC GAT AAA CTA TTC TAC AAT GCA CCG AAA ATG gly glu pro val leu ash phe ala ile val asp lys leu phe tyr ash ala pro lys met

341/281

TOT CTT CTG GAT TAT CTT CTC CTA ATT GTC GAC CCC CAG TCG TGT AAC GAT GAT GTA CGA ser leu leu asp tyr leu leu leu ile val asp pro gin ser cys asn asp asp val arg

901/301

AAA GAT CTT AAA ACA AAA CTG ATG GCG GGA AAA ATG ACA ATC AGA CAA GCC GCG CGA lys asp leu lys thr lys leu met ala gly lys met thr ile arg gln ala ala arg pro

961/321

AGA ATT CGA CAA TTA TTG GAA AAT TTG AAG CTG AAA TGC GCA GAA GTT TGG GAT AAC GAA arg ile arg gln leu leu glu asn leu lys leu lys cys ala glu val trp asp asn glu

1021/341

ATG TCG AGA TTG ACA GAA CGA CAT CTG ACA TTT CTA GAT TTG TGC GAG GAA AAC TCT CTT met ser arg leu thr glu arg his leu thr phe leu asp leu cys glu glu ash ser leu

1081/361

GTT TAT AAA GTC ACT GGT AAA TCG GAC AGA GGA AGA AAT GCA AAA AAG TAC GAT ACT ACA val tyr lys val thr gly lys ser asp arg gly arg asn ala lys lys tyr asp thr thr

1141/381

TTG TTC AAA ATC TAT GAG GAA AAC AAA AAG TTC ATT GAG TTT CCC CAC CTA CCA CTA GTC leu phe lys ile tyr glu glu asn lys lys phe ile glu phe pro his leu pro leu val

1201/401

AAA GTT AAA AGT GGA GCA AAA GAA TAC GCT GTA CCA ATG GAA CAT CTT GAA GTT CAT GAG lys val lys ser gly ala lys glu tyr ala val pro met glu his leu glu val his glu

1261/421

AAG CCA CAA AGA TAC AAG AAT CGA ATT GAT CTG GTG ATG CAA GAC AAG TTT CTA AAG CGA lys pro gin arg tyr lys asm arg ile asp leu val met gin asp lys phe leu lys arg

1321/441

GCT ACA CGA AAA CCT CAC GAC TAC AAA GAA AAT ACC CTA AAA ATG CTG AAA GAA TTG GAT ala thr arg lys pro his asp tyr lys glu asn thr leu lys met leu lys glu leu asp

1381/461

TTC TCT TCT GAA GAG CTA AAT TTT GTT GAA AGA TTT GGA TTA TGC TCC AAA CTT CAG ATG phe ser ser glu glu leu asn phe val glu arg phe gly leu cys ser lys leu gln met

1441/481

ATC GAA IGT CCA GGA AAG GTT TTG AAA GAG CCA ATG CTT GTG AAT AGT GTA AAT GAA CAA ile glu cys pro gly lys val leu lys glu pro met leu val asn ser val asn glu gln

1501/501

ATT AAA ATG ACA COA GTG ATT CGT GGA TTT CAA GAA AAA CAA TTG AAT GTG GTT CCC GAA ile lys met thr pro val ile arg gly phe gln glu lys gln leu asn val val pro glu

FIG. 6B

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AAA GAA OTT IGO IGT GOT GIT ITT GIA GIC AAC GAA ACA GOG GGA AAI COA IGO ITA GAA Lys glu leu cys cys ala val phe val val asn glu thr ala gly asn pro cys leu glu

1621/541 GAG AAC GAC GIT GIT AAG ITO TAC ACC GAA CTA AIT GGT GGT TGC AAG ITC CGT GGA ATA glu asn asp val val lys one tyr thr glu leu ile gly gly cys lys phe arg gly ile

1681/561

CGA ATT GGT GCC AAT GAA AAC AGA GGA GCG CAA TCT ATT ATG TAC GAC GCG ACG AAA AAT arg ile gly ala asn glu asn arg gly ala gin ser ile met tyr asp ala thr lys asn

1741/581

GAA TAT GCC TTC TAC AAA AAT TGT ACA STA AAT ACC GGA ATC GGT AGA TTT GAA ATA GCC glu tyr ala phe tyr lys asn cys thr leu asn thr gly ile gly arg phe glu ile ala

1901/601

GCA ACA GAA GCG AAG AAT ATG TTT GAA CGT CTT CCC GAT AAA GAA CAA AAA GTC TTA ATG ala thr glu ala lys asn met phe glu arg leu pro asp lys glu gln lys val leu met

1861/621

ITC ATT ATC ATT TOO AAA IGA CAA CTG AAT GCT TAC GGT TTT GTG AAA CAT TAT TGC GAT phe ile ile ser lys arg gln leu asn ala tyr gly phe val lys his tyr cys asp

CAC ACC ATC GGT GTA GCT AAT CAG CAT ATT ACT TCT GAA ACA GTC ACA AAA GCT TTG GCA his thr ile gly val ala asn gin his ile thr ser glu thr val thr lys ala leu ala

TCA CTA AGG CAC GAG AAA GGA TCA AAA CGA ATT TTC TAT CAA ATT GCA TTG AAA ATC AAC ser leu arg his glu lys gly ser lys arg ile phe tyr gln ile ala leu lys ile asn

2041/681

GCG AAA TTA GGA GGT ATT AAC CAG GAG CTT GAC TGG TCA GAA ATT GCA GAA ATA TCA CCA ala lys leu gly gly ile asn gln glu leu asp trp ser glu ile ala glu ile ser pro

1101/701

JAA GAA ARA GAA AGA CGG ARA ACA ATG CCA TTA ACT ATG TAT GTT GGA ATT GAT GTA ACT giu glu lys glu arg arg lys thr met pro leu thr met tyr val gly ile asp val thr

2161/721 2191/731

CAT CCA ACC TCC TAC AGT GGA ATT GAT TAT TCT ATA GCG GCT GTA GTA GCG AGT ATC AAT his pro thr ser tyr ser gly ile asp tyr ser ile ala ala val val ala ser ile asn

2221/741

CCA GGT GGA ACT ATC TAT CGA AAT ATG ATT GTG ACT CAA GAA GAA TGT CGT CCC GGT CAG pro gly gly thr ile tyr arg asn met ile val thr gln glu glu cys arg pro gly glu

2281/761

IGT GCA GTG GCT CAT GGA IGG GAA AGA ACA GAT ATT TTG GAA GCA AAG ITC GTG AAA ITG arg ala val ala his giy arg glu arg thr asp ile leu glu ala lys phe val lys leu

CTO AGA GAA TTO GCA GAA AAC AAC GAC AAT OGA GCA COA GCG CAT ATT GTA GTO TAT OGA leu arg glu phe ala glu asn asn asp asn arg ala pro ala his ile val val tyr arg

FIG. 6C



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2401/801 SAC SGA STT AGC SAT TOS SAG ATG CTA OST STT AGT CAT SAT SAG CTT CGA TOT TTA AAA asp gly val ser asp ser glu met leu arg val ser his asp glu leu arg ser leu lys AGC GAA GTA AAA CAA TTO ATG TOG GAA CGG GAT GGA GAA GAT CCA GAG CCG AAG TAC ACG ser glu vai lys gin phe met ser glu arg asp gly glu asp pro glu pro lys tyr thr TTC ATT GTG ATT CAG AAA AGA CAC AAT ACA CGA TTG CTT CGA AGA ATG GAA AAA GAT AAG phe ile val ile gin lys arg his asn thr arg leu leu arg arg met glu lys asp lys CCA GTG GTC AAT AAA GAT CTT ACT CCT GCT GAA ACA GAT GTC GCT GTT GCT GCT GTT AAA pro val val asn lys asp leu thr pro ala glu thr asp val ala val ala val lys CAA TGG GAG GAT ATG AAA GAA AGC AAA GAA ACT GGA ATT GTG AAC CCA TCA TCC GGA gln trp glu glu asp met lys glu ser lys glu thr gly ile val asn pro ser ser gly ACA ACT GTG GAT AAA CTT ATC GTT TCG AAA TAC AAA TTC GAT TTT TTC TTG GCA TCT CAT thr thr val asp lys leu ile val ser lys tyr lys phe asp phe phe leu ala ser his 2761/921 CAT GGT GTC CTT GGT ACA TCT CGT CCA GGA CAT TAC ACT GTT ATG TAT GAC GAT AAA GGA his gly val leu gly thr ser arg pro gly his tyr thr val met tyr asp asp lys gly ATG AGC CAA GAT GAA GTC TAT AAA ATG ACC TAC GGA CTT GCT TTT CTC TCT GCT AGA TGT met ser gln asp glu val tyr lys met thr tyr gly leu ala phe leu ser ala arg cys CGA AAA CCC ATC TCG TTG CCT GTT CCG GTT CAT TAT GCT CAT TTA TCA TGT GAA AAA GCG arg lys pro ile ser leu pro val pro val his tyr ala his leu ser cys glu lys ala AAA GAG CTT TAT CGA ACT TAC AAG GAA CAT TAC ATC GGT GAC TAT GCA CAG CCA CGG ACT Lys glu leu tyr arg thr tyr lys glu his tyr ile gly asp tyr ala gin pro arg thr CGA CAC GAA ATG GAA CAT TIT CTC CAA ACT AAC GTG AAG TAC CCT GGA ATG TCG TTC GCA arg his glu met glu his phe leu gln thr asn val lys tyr pro gly met ser phe ala TAA CAT TIT GCA AAA GTG TCG CCC GTT TCA ATC AAA TTT TTC AAT TGT AGA TAT TGT ACT TAC TIT TIT TIA AAG CCC GGT TIC AAA AAT TCA TIC CAT GAC TAA CGT TIT CAT AAA TIA

FIG. 6D

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CTT GAA ATT TAA AAA AAA AAA AAA AAA (SEQ ID NO:2)



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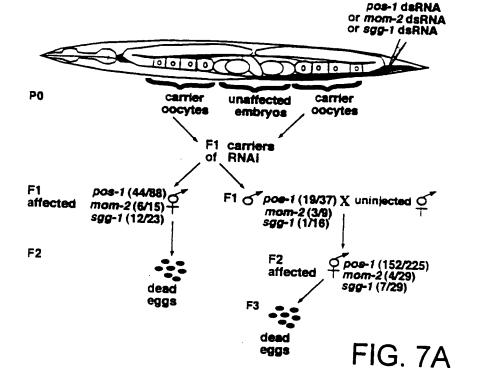
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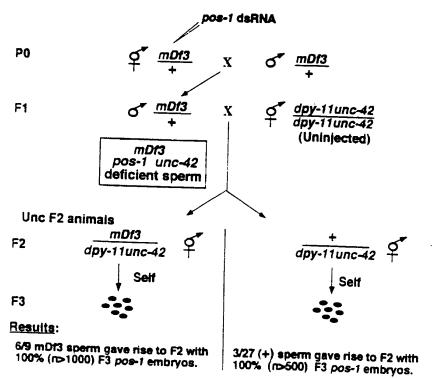


FIG. 7B

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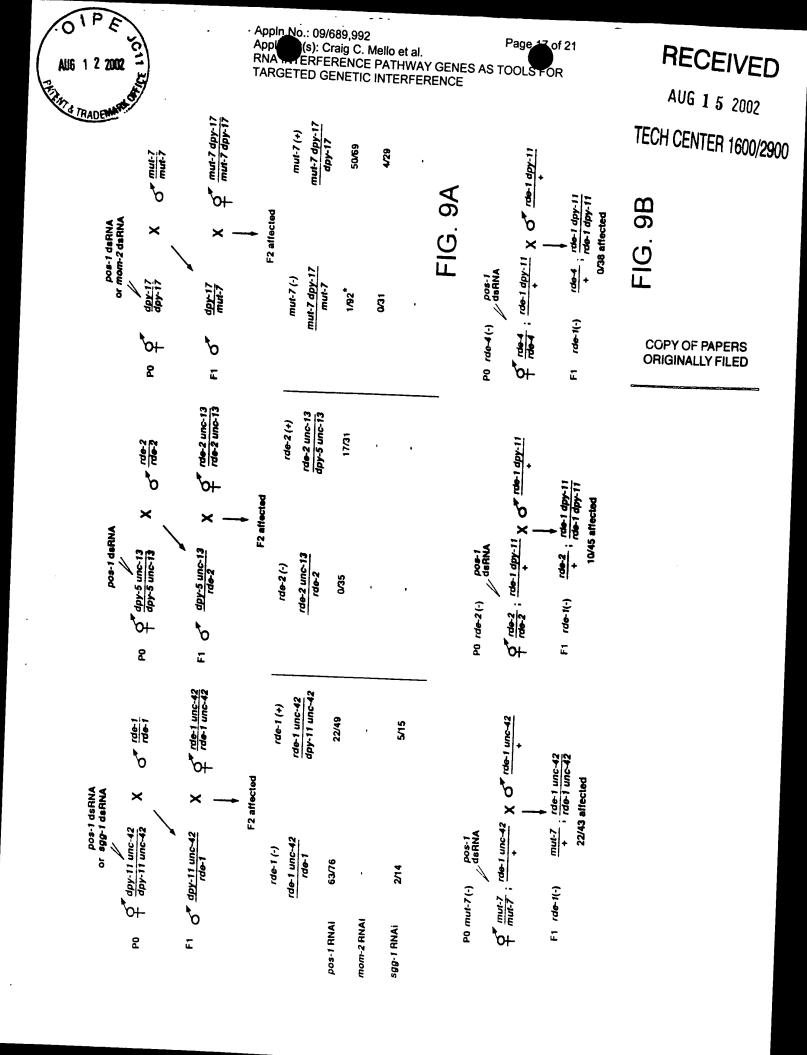
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				•
	Injecte	d PO	F1	
	po // de	e-1 RNA		
	rde-1 unc	-42	rde-1 (-)	11/24
	//		1X rde-1 (+)	9/72
	rde-2 unc	-13	rde-2(-) rde-2(+)	0/39
	//		750-2 (+)	23/78
	mut-7 dpy-	· <u>1</u> 7	mut-7(-)	0/15 20/50
	_ //		(1)	-000
	rde-4 unc-	<u>69</u>	rde-4 (-)	5/15
FIG.	8A		rde-4 (+)	11/48
	PO		injected F1	ļ
			pos-1 derna	
	rde-1 unc-	<u>12</u>	rde-1 unc-42	0/37
	Comments of the	••		
	orde-4 unc-4	<u> </u>	rde-4 unc-69	0/37
	OD			

FIG. 8B





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10 20 30 40 50 60 ATGGATTTAACCAAACTAACGTTTGAAAGCGTTTTCGGTGGATCAGATGTTCCTATGAAG M D L T K L T F E S V F G G S D W
M D L T K L T F E S 'Y F G G S D V P M K
70
70 80 90 100 110 120 PSRSEDNKTPRNRTTGAGATTTCTG
P S R S E D N K T P R N R T D L E M F L
130
130 140 150 160 170 180 AAGAAAACTCCCCTCATGGTACTAGAAGAGGCTGCTAAGGCTGTCTATCAAAAGACGCCA K K T P L M V L E E À À K À V CAAAAGACGCCA
K K T P L M V L E E À A K A V Y Q K T P
190 205
190 200 210 220 230 240 ACTTGGGGCACTGTCGAACTTCCTGAAGGCTTCGAGATGACGTTGAATCTGAATGAA
T W G T V E L P E G F E M T L I L N E I
250 250
250 260 270 280 290 300 T V K G Q A T S K K A A R O K
T V K G Q A T S K K A A R Q K A A V E Y
310 202 X A A V E Y
310 320 330 340 350 360 TTACGCAAGGTTGTGGAGAAAGGAAAGCACGAAATCTTTTTCATTCCTGGAACAACCAAA L R K V V E K G K H E I F F I
L R K V V E K G K H E I F F I P G T T K
370 and
370 380 390 400 410 420 GAAGAAGCTCTTTCGAATATTGATCAAATATCGGATAAGGCTGAGGAATTGAAACGATCA E E A L S N I D Q I S D K A F
E E A L S N I D Q I S D K A E E L K R S
430 440 450 460 470 480 ACTICAGATGCTGTTCAGGATAACGATAACGATGATTCGATTC
T S D A V Q D N D N D D S I P T S A E F
490 500 510 520 530 540 CCACCTGGTATTTCGCCAACCGAGAATTGGGTCGGAAAGTTGCAGGAAAATCTCAAAAA P P G I S P T E N W 7 G K L O F
F E N W 7 G K L O F WALL CHAAAAA
550 560 570 580 590 600
AGCAAGCTGCAAGCCCCAATCTATGAAGATTCCAAGAATGAGAGAACCGAGCGTTTCTTG S K L Q A P I Y E D S K N E R T
S K L Q A P I Y E D S K N E R T E R F L
311 (36
V I C T M C N Q K T R G I R S K K K D A
K N L A A W L M W K A L E D G I E S L E
S Y D M V D V I E N L E E A E H L L E I
FIC 10A

FIG. 10A



Applin No.: 09/689,992

Applicant(s): Craig C. Mello et al.

RESTANCE PATHWAY GENES AS TOOLS FOR TARGETED GENETIC INTERFERENCE

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FIG. 10B



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